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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/726,366	12/03/2003	Claudio Soto-Jara	009621-34567 DIV	8149

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	**PAPER NUMBER**
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/726,366	SOTO-JARA, CLAUDIO	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 18-28* is/are pending in the application.

4a) Of the above claim(s) *1-11,13,14,19-21,25 and 26* is/are withdrawn from consideration.

5)☒ Claim(s) *27 and 28* is/are allowed.

6)☒ Claim(s) *12,18 and 22-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *1-14 and 18-28* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 25 October 2006 has been entered in full. Claims 12, 22, 27, and 28 are amended. Claims 15-17 are cancelled.

Claims 1-11, 13-14, 19-21, and 25-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 23 August 2005.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 12, 18, 22-24, 27, and 28 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to claims 12, 22, 27, and 28 at pg 3 of the previous Office Action (25 May 2006) are *withdrawn* in view of the amended claims (25 October 2006).

Double Patenting

2. Claims 12, 18, and 22-24 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4, 6, 8, 10, 11, and 13 of U.S. Patent No. 5,948,763 in view of Findeis et al. (WO 96/28471). The basis for this rejection is set forth at pg 4-6 of the previous Office Action (25 May 2006).

Applicant's arguments in the response submitted 25 October 2006 as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At pg 14 of the Response, Applicant asserts that the ODP rejection is improper as the '763 patent issued prior to the earliest claimed priority date of the present application. Applicant argues that the '763 patent cannot form the basis of an ODP rejection because it qualifies as prior art at least in that the patent was granted before the earliest effective filing date of the present application.

Applicant's argument has been fully considered but is not found to be persuasive. Specifically, according to MPEP § 804(I)(A), "[d]ouble patenting may exist between an issued patent and an application filed by the same inventive entity, or by a different inventive entity having a common inventor, and/or by a common assignee/owner". See also MPEP § 804, chart II-B.

(ii) At pg 15 of the Response, Applicant contends that neither the '763 patent, or Findeis et al., teach or suggest, alone or in combination, the superiority of the claimed sequence or that the claimed chemical modifications would increase stability, particularly since the mechanism of degradation was unknown at the time. Applicant submits that only through the use of impermissible hindsight may a person of ordinary skill in the art identify the desirability of the presently claimed sequence and chemical modifications. Applicant also asserts that a person of ordinary skill in the art is provided no motivation by the '763 patent to identify the presently claimed sequence, chemically modify that sequence, or a reasonable expectation that the modifications would increase stability *in vivo* and retain *in vivo* function. Applicant states that Findeis et al. does not teach or suggest that chemical modification of the claimed sequence would increase stability without compromising the function *in vivo*. Applicant concludes that

there is no motivation to combine references. Applicant indicates that modification of a peptide sequence could adversely affect its function.

Applicant's arguments have been fully considered but is not found to be persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). As indicated in the previous Office Action of 25 May 2006, the patented claims which recite methods of reducing the formation or amount of amyloid or amyloid-like deposits comprising contacting the amyloid protein with an inhibiting peptide comprising a portion of three to eight amino acids, which portion is hydrophobic and has one or more proline residues therein, said inhibitory peptide having a length of three to fifteen amino acids render obvious the pending claims of methods of reducing the formation or amount of amyloid or amyloid-like deposits comprising contacting the amyloid protein with a peptide consisting of SEQ ID NO: 1 (Leu-Pro-Phe-Phe-Asp) which is chemically modified. The patented claims also recite that at least some of the amino acid residues are D-amino acid residues. The patented claims also recite that the inhibitory peptide has the sequence of SEQ ID NO: 18 (Leu-Pro-Phe-Phe-Asp), which is SEQ ID NO: 1 of the instant application.

Although the '763 patent does not teach that the inhibiting peptide is chemically modified, Findeis et al. teach a peptide that binds to natural β amyloid peptides, modulates the

aggregation of natural β amyloid peptides, and that the peptide may be modified at the amino terminus, carboxy terminus, or both, with such groups as amide groups, alkyl or aryl amide groups, and hydroxyl groups (pg 3-6, 11, 14, last paragraph through pg 15). Findeis et al. teach a method for inhibiting the formation of natural β-amyloid peptide deposits comprising contacting the natural β-amyloid peptides with a modified modulator peptide such that aggregation of the natural β-amyloid peptides is inhibited (pg 6, lines 24-30; pg 37; pg 39, lines 8-36). Findeis et al. state that the method may be used to treat clinical occurrences of β amyloid deposition, such as Alzheimer's disease and Down's syndrome (pg 40, lines 11-20).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the '763 patent and Findeis et al. teach that the amyloid beta protein plays a role in the pathogenesis of Alzheimer's disease ('763 col 1-2; Findeis et al. pg 1), with Findeis et al. additionally teaching that short, chemically modified inhibitory beta amyloid peptides have increased stability, bioavailability, and solubility (Findeis et al. pg 13, lines 13-15). For instance, Findeis et al. disclose that a beta amyloid modulator compound is modified to alter a pharmacokinetic property of the compound, such as *in vivo* stability or half-life (pg 28, lines 25-27). Findeis et al. continue to state that "preferred C-terminal modification include those which reduce the ability of the compound to act as a substrate for carboxypeptidases. Examples of

preferred C-terminal modifiers include an amide group, an ethylamide group and carious non-natural amino acids, such as D-amino acids and β-alanine. Alternatively, when the modifying group is attached to the carboxy-terminal end of the aggregation core domain, the amino-terminal end of the compound can be further modified, for example, to reduce the ability of the compound to act as a substrate for aminopeptidases" (pg 28, lines 38-39 through pg 29, lines 1-5). Furthermore, Findeis et al. clearly teach that their modified beta amyloid modulator peptides (1) inhibit beta amyloid aggregates *in vitro* and (2) inhibit beta amyloid neurotoxicity of cultured neuronal cells (pg 68-74; Figures 3-4). The person of ordinary skill in the art reasonably would have expected success because similar chemical modifications of peptides to increase stability, bioavailability, and permeability were already being performed at the time the invention was made. Therefore, the instant claims reciting a method for reducing the formation of amyloid or amyloid-like deposits involving abnormal folding into β sheet structuring comprising bringing into the presence of said amyloid β peptide an effective amount of a peptide analog generated by chemical modification of the peptide consisting of SEQ ID NO: 1 (Leu-Pro-Phe-Phe-Asp) is not patentably distinct over the issued claims in U.S. Patent No. 5,948,763 in view of Findeis et al.

Claim Rejections - 35 USC § 103

3. Claims 12, 18, and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Findeis et al. (WO 96/28471) in view of Soto et al. (Nat Med 4(7): 822-826, July 1998). The basis for this rejection is set forth at pg 6-7 of the previous Office Action (25 May 2006).

Applicant's arguments in the response submitted 25 October 2006 as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At pg 16 of the Response, Applicant contends that Soto et al. does not provide a motivation to chemically modify the presently claimed sequence. Applicant states that Soto et al. discusses the need to test the chemical modification of a peptide. Applicant adds that Findeis et al. does not teach or suggest chemical modification of the claimed sequence, or that it would increase the stability of the claimed peptide without compromising the function *in vivo*. Applicant argues that only the present specification provides *in vivo* data demonstrating that chemical modification produces a product having increased stability and retaining activity *in vivo*, the cited references to not provide a motivation to chemically modify the claimed sequence.

Applicant's arguments have been fully considered but are not found to be persuasive. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Soto et al. and Findeis et al. teach that amyloid beta protein plays role in the pathogenesis of Alzheimer's Disease and that short, chemically modified inhibitory beta amyloid peptides have increased stability, bioavailability, and solubility (Soto et al., pg 822, col 1 and pg 823, col 2; Findeis et al. pg 1 and pg 13, lines 13-15).

Specifically, Soto et al. teaches that one of the drawbacks with the *in vivo* utilization of peptides is that they are degraded by natural enzymes and have poor blood-brain barrier permeability (pg 823, col 2, 1st full paragraph). Soto et al. continue to disclose that they recently

designed chemical modifications of a beta-sheet breaker peptide that did not alter its activity *in vitro*, and actually increased its brain permeability and resistance to proteolysis in rat plasma (pg 823, col 2, 1st full paragraph). Furthermore, Findeis et al. clearly teach that their modified beta amyloid modulator peptides (1) inhibit beta amyloid aggregates *in vitro* and (2) inhibit beta amyloid neurotoxicity of cultured neuronal cells (pg 68-74; Figures 3-4). Findeis et al. disclose that a beta amyloid modulator compound is modified to alter a pharmacokinetic property of the compound, such as *in vivo* stability or half-life (pg 28, lines 25-27). Findeis et al. continue to state that "preferred C-terminal modification include those which reduce the ability of the compound to act as a substrate for carboxypeptidases. Examples of preferred C-terminal modifiers include an amide group, an ethylamide group and carious non-natural amino acids, such as D-amino acids and β-alanine. Alternatively, when the modifying group is attached to the carboxy-terminal end of the aggregation core domain, the amino-terminal end of the compound can be further modified, for example, to reduce the ability of the compound to act as a substrate for aminopeptidases" (pg 28, lines 38-39 through pg 29, lines 1-5). The person of ordinary skill in the art reasonably would have expected success because non-chemically modified iAβ5 (as taught by Soto et al.) reduced amyloid beta deposition *in vivo* (Soto et al.; pg 823, col 1) and similar chemical modifications of peptides to increase stability, bioavailability, and permeability were already being performed at the time the invention was made (for example, Soto et al., pg 823, col 2; Findeis et al., pg 68-74). Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

Conclusion

Claims 27 and 28 are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
16 January 2007

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud